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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,272	11/22/2004	Domenico Maglione	10500-008	4002

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EXAMINER	
TSAY, MARSHA M	
ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,272	MAGLIONE ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received March 20, 2007. Claims 1-15 are canceled. Claims 16-35 are pending and currently under examination.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Priority: The priority date is March 5, 2002.

Objections and Rejections

Claim 27 is objected to because of the following informalities: claim 27 recites "1, 10 μg/Kg/day to 200 μg/Kg/day." The numeral "1" needs to be deleted. Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex*

parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 28-29 recite the broad recitation 1 to 500 μg/Kg/day, and the claim also recites 10 μg/Kg/day to 200 μg/Kg/day which is the narrower statement of the range/limitation.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-35 remain rejected again under 35 U.S.C. 102(b) as being anticipated by Ziche et al. (1997 Lab. Invest. 76(4): 517-531). Ziche et al. teach PIGF-1 protein was purified mostly as homodimeric glycosylated protein and was approximately 0.17 mg/l of conditioned medium (p. 528; claims 30-35). Densitometric scanning of the stained gels revealed that 0.4%, 86.3%, and 13.2% of the total protein corresponded with monomeric, dimeric, and trimeric forms of PIGF-1, respectively (p. 518; claims 30-35). On page 528, col. 2, Ziche et al. teach affinity-purified PLGF-1 antibodies were obtained from the immune rabbit serum as described by Maglione et al. (1991 PNAS 88: 9267-9271). As described in the Maglione et al. reference, two

rabbits were immunized with a total of 300 ug antigen (purified PLGF-1), therefore Maglione et al. teach a composition comprising 0.3 mg PLGF-1 (p. 9268 Maglione et al.).

In their remarks, Applicants assert that claim 30 seeks protection for a pharmaceutical composition comprising PLGF-1, essentially in dimeric form, as active principle in an amount of 0.1 to 10 mg per gram of topical composition, whereas claim 31 seeks protection for a cosmetic composition comprising from 0.01 mg (10^4 ng) to 0.09 mg ($9x10^4$ ng) per gram of composition. Applicants further assert that Ziche et al. disclose PLGF-1 compositions in the form of implants or solutions comprising no more than 200 ng/pellet (i.e. dosage unit) or 180 ng/mL solution (p. 518 or p. 521). Therefore, the highest amounts disclosed by Ziche et al. are lower than the amounts defined in instant claims 30-31. Applicants arguments have been fully considered but they are not persuasive.

The instant claims 30-31 are drawn to a composition comprising PLGF-1, essentially in dimeric form, as active principle in an amount of 0.1 to 10 mg per gram of topical composition and /or 0.01 mg to 0.09 mg per gram of topical composition, respectively. Claims 32-33 further limit the PLGF-1 composition to topical forms, i.e. solution, lotion, gel, cream, paste, etc. As noted above, Ziche et al. teach a composition in solution form comprising PLGF-1, wherein at least 98.5% of the PLGF is in active dimeric and multimeric form, at least 70% is in dimeric form and no more than 1.5% is in monomeric form as noted by the densitometric scanning data (0.4% monomeric, 86.3% dimeric, 13.2% trimeric) (p. 518). Ziche et al. further teach affinity-purified PLGF-1 antibodies were obtained from immune rabbit serum as described by Maglione et al. (1991 PNAS), which teach an adjuvant solution comprising 0.3 mg PLGF-1 (p. 9268

Maglione et al.). Therefore, Ziche et al., by incorporation of the Maglione et al. reference, teach a composition comprising PLGF-1, essentially in dimeric form, as an active principle, in an amount that meets the dosage units of the instant claim 30 (0.1 mg to 10 mg per gram). Ziche et al. also teach PIGF-1 protein was purified mostly as homodimeric glycosylated protein at a concentration of approximately 0.17 mg/l of conditioned medium (claim 31). Therefore, the instant claims are still anticipated by Ziche et al. because Ziche et al. teach a solution comprising PLGF-1 in active dimeric and multimeric form and said solution is inherently a topical composition.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-22, 23-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ziche et al. (1997 Laboratory Investigation 76(4): 517-531) in view of Failla et al. (2000 J. Invest. Dermatology 115(3): 388-395). The teachings of Ziche et al. are outlined above. While Ziche et al. teach promotion of angiogenesis with PLGF-1, Ziche et al. do not teach the application of PLGF-1 in the treatment of a state selected from the group consisting of diseases involving cutaneous or subcutaneous connective tissue, scleroderma, and early skin aging due to exposure to atmospheric aggressive agents.

Failla et al. (2000 J. Invest. Derm. 115(3): 388-395) teach PLGF-1 is induced in human keratinocytes during wound healing. Fallia et al. teach PLGF-1 is expressed *in vivo* by migrating

keratinocytes at the wound site (p. 391). The involvement of PLGF in wound healing was tested by analyzing its expression in human full-thickness wounds *in vivo* (p. 391). Failla et al. teach their data demonstrate that keratinocytes are a source of PLGF during wound healing *in vivo* and indicate a role for PLGF-1 in the neoangiogenesis process associated with cutaneous wound repair (p. 388, abstract).

It would have been obvious to a person having ordinary skill in the art to formulate the PLGF-1 composition of Ziche et al. and use it in promoting angiogenesis in the treatment of an alteration involving skin tissue (claims 16-22) in view of Failla et al. because Failla et al. teach and suggest a role for PLGF-1 in the neoangiogenesis process associated with cutaneous wound repair. One of ordinary skill in the art would be motivated to apply the PLGF-1 composition of Ziche et al. in view of Failla et al. to a skin alteration and expect it to have a reasonable level of success because Failla et al. disclose PLGF-1 has a role in cutaneous wound repair and its addition to a skin alteration would help to expedite the healing process.

It would also have been obvious to a person having ordinary skill in the art to apply the PLGF-1 composition of Ziche et al. and use it for the cosmetic treatment of an adult (claims 23-29) in view of Failla et al. because Failla et al. teach and suggest a role for PLGF-1 in the neoangiogenesis process associated with cutaneous wound repair. One of ordinary skill in the art would be motivated to apply the PLGF-1 composition of Ziche et al. in view of Failla et al. for the treatment of natural skin again and hair loss in an adult and expect it to have a reasonable level of success because these conditions are known in the art to be skin diseases and/or disorders and Failla et al. disclose PLGF-1 has a role in cutaneous wound repair and its addition to a skin alteration would help to expedite the healing process.

In their remarks received March 20, 2007, Applicants again note that the target diseases of the instant invention are related to alterations of the connective tissues and are characterized by fibroblast activation and excessive production and deposit of sclerotized collagen with formation of fibrosis and calcification zones. (1) Ziche et al. discloses the ability of PLGF-1 to elicit angiogenesis in two animal models: the rabbit cornea and the chicken chorioallantoic membrane. Applicants assert that this is a simple biological activity developed on normal (healthy) rabbit cornea or chorioallantoic membrane, which are endothelial tissues, which cannot be confused with a pharmacological, therapeutic effect, that necessarily implies the capability of correcting and recovering an abnormal situation. Moreover, the activity reported by Ziche et al. concerns endothelial cells, not connective tissues. Regarding (2) the Failla et al. reference, Applicants assert Failla et al. teach that native PLGF is induced in human keratinocytes during wound healing and demonstrates that PLGF plays a role in the neoangiogenesis process associated with wound repair. Applicants further assert that the definition of a "wound" is different from the pathological states of scleroderma and the other connective tissue diseases according to the invention. Wounds are normally due to external agents, which are not comparable to the impaired metabolism resulting in the production and deposit of sclerosed collagen in the connective tissues. Applicants also assert that while Failla et al. indicate a role of PLGF in cutaneous wound repair, Failla et al. do not demonstrate that PLGF has any active function in the healing. In other words, the Failla et al. reference fails to show that the induced PLGF is the factor causing the healing rather than simply being a side effect of the wound or a marker. Applicant's arguments have been fully considered but they are not persuasive.

It should first be noted that instant claim 16 has currently been amended to include the limitations of "an individual in need thereof" and the dosage unit of "1 to 500 μg per Kg of body per day." The claim is still drawn to a method of treatment of a state, wherein the state is selected from diseases and pathological alterations involving the cutaneous or subcutaneous connective tissue, scleroderma, and early skin aging due to exposure to atmospheric agents or to protracted solar irradiation.

In response to Applicants' first remarks regarding the Ziche et al. reference, it should be noted that Ziche et al. was merely cited to document that pharmaceutical compositions of PLGF were prepared and known in the art. Ziche et al. teach compositions comprising PLGF-1 in active dimeric and multimeric form, as active principle, that meet the instant dosage units. The Failla et al. reference overcomes the deficiency of the Ziche et al. reference because it discloses PLGF-1 has an active role in the neoangiogenesis process associated with cutaneous wound repair.

With respect to Applicants' second argument regarding the Failla et al. reference and the definition of "wound", it should be noted that the definition of "wound" does encompass the pathological states of scleroderma and the other connective tissue diseases according to the invention and as currently recited in instant claim 16. It is well known in the art that a wound is a disruption in the continuity of cells. Therefore, regardless of the degree of the injury or whether if it is an acute wound injury or a chronic wound injury, the wound injury is still identified as a disruption in the continuity of cells. Claim 16 recites the state can be selected from diseases and pathological alterations involving the cutaneous or subcutaneous connective

tissue and/or early skin aging due to exposures to atmospheric aggressive agents or to protracted sun irradiation. Such states can include sunburns, bed sores, and/or ulcerations (University of Maryland, DermIS reference sheets), which are all wounds because they all involve an injury characterized by broken skin. Additionally, these states can clearly be seen to be encompassed by the states recited in claim 16 because they are diseases and/or pathological alterations involving the cutaneous or subcutaneous tissue, and/or conditions resulting from exposure to atmospheric aggressive agents. Therefore, one of ordinary skill in the art would be motivated to use the composition of PLGF-1 of Ziche et al. to treat a skin alteration and/or skin aging due to solar irradiation because Failla et al. disclose a role for PLGF-1 in the neoangiogenesis process associated with a skin alteration, i.e. a cutaneous wound repair.

Regarding Applicants assertion that while the Failla et al. reference indicates a role of PLGF in cutaneous wound repair, Failla et al. do not demonstrate that PLGF has any active function in the healing, this is not believed to be persuasive. On page 394, Failla et al. discloses that their data indicate that PLGF is actively involved in angiogenesis associated with wound repair. Therefore, it would appear that PLGF is indeed a factor causing the healing and/or is involved in the wound healing process rather than simply being a side effect of the wound or a marker. Therefore, the Failla et al. reference supplements the Ziche et al. reference and indicates that PLGF-1 does have a pharmacological and therapeutic effect in wound healing.

With respect to Applicants' assertions that neither skin aging nor hair loss is correlated or comparable to wound and/or wound-healing, one of ordinary skill would recognize that sunburns, as noted above, can be associated with skin aging and hair loss is closely associated with skin diseases. Therefore, one of ordinary skill would be motivated to apply the PLGF-1

composition of Ziche et al. and use it for the cosmetic treatment of an adult in view of Failla et al. because Failla et al. teach PLGF-1 is actively involved in the neoangiogenesis process associated with cutaneous wound repair.

The rejection of claims 16-29 under 35 U.S.C. 103(a) as being unpatentable over Ziche et al. (1997 Laboratory Investigation 76(4): 517-531) in view of Failla et al. (2000 J. Invest. Dermatology 115(3): 388-395) is maintained.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

May 17, 2007

M. Monshi
MARYAM MONSHIPOURI, PH.D.
PRIMARY EXAMINER